Clinical Pain Research

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Granisetron vs. lidocaine injection to trigger points in the management of myofascial pain syndrome: a double-blind randomized clinical trial

https://doi.org/10.1515/sjpain-2020-0154
Received October 4, 2020; accepted January 12, 2021; published online March 10, 2021

Abstract

Objectives: Granisetron and lidocaine injections have been used for the management of myofascial pain syndrome. This study was aimed to compare the efficacy of granisetron and lidocaine injections to trigger points of upper trapezius in the management of myofascial pain syndrome.

Methods: We performed a double-blind randomized clinical trial in an outpatient clinic of physical medicine and rehabilitation at a teaching hospital. A total of 40 patients aged ≥18 with neck pain due to myofascial pain syndrome were included. They had pain for at least one month with the intensity of at least 30 mm on a 100 mm visual analog scale. Each participant received a single dose of 1 mL lidocaine 2% or 1 mg (in 1 mL) granisetron. The solutions were injected into a maximum of three trigger points of the upper trapezius. We instructed all patients to remain active while avoiding strenuous activity for three or four days, and to perform stretch exercise and massage of their upper trapezius muscles. We assessed the patients before the interventions, and one month and three months post-injection. The primary outcome was the Neck Disability Index and the secondary outcome was the Neck Pain and Disability Scale.

Results: Both interventions were successful in reducing neck pain and disability (all p-values <0.001). However, the neck pain and disability responded more favorably to lidocaine than granisetron (p=0.001 for Neck Disability Index, and p=0.006 for Neck Pain and Disability Scale). No significant side-effect was recognized for both groups.

Conclusions: Both lidocaine and granisetron injections to trigger points are effective and safe for the management of the syndrome and the benefits remain at least for three months. However, lidocaine is more effective in reducing pain and disability. The injections are well-tolerated, although a transient pain at the site of injections is a common complaint. One mL of lidocaine 2% is more effective than 1 mg (in 1 mL) granisetron for injecting into the trigger points of the upper trapezius in myofascial pain syndrome.

Keywords: granisetron; lidocaine; myofascial; neck; pain; trigger point.

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Introduction

Myofascial Pain Syndrome (MPS) is a common, chronic, and regional musculoskeletal condition [1]. The prevalence of MPS has been estimated at 15% in general medical centers and 85% in pain clinics [1, 2]. It has a socioeconomic burden by causing limitations in performing physical activities [2]. Patients with MPS experience local pain or pain within zones of referral at rest or during movement

[3]. In addition to an achy and diffused pain, typical patients have palpable and tender nodules within taut bands of engaged muscles known as trigger points [2, 4].

Dry needling, as well as wet needling, is commonly used in the clinic [4]. For dry needling, a thin needle is inserted into the muscle to inactivate trigger points through mechanical irritation [5]. For wet needling, local anesthetics, corticosteroids, botulinum toxin type A, sclerosing agents, or saline solution are injected into the points [4, 6]. Injection of lidocaine (0.5–2%) or procaine (1%) is a common method of wet needling [6].

The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) is a mediator of inflammation released from platelets and mast cells following tissue damage [7]. It is believed that 5-HT_3 receptor blockade decreases chronic muscle pain. A trial showed that three days of oral administration of granisetron, a 5-HT_3 antagonist, increased the pressure pain threshold over healthy trunk and limb muscles [8]. Local administration of granisetron also reported to decrease 5-HT [9], and hypertonic saline [10] induced pain, allodynia, and hyperalgesia in the masseter muscle of human subjects.

Researchers sought if repeated intramuscular tender-point injections of granisetron reduce pain in patients with myofascial temporomandibular disorders. A recent meta-analysis of needling therapies for MPS of masticatory muscles showed that granisetron favorably affected pain intensity in the short- (immediate to three weeks post-intervention) and intermediate-term (one to six months post-intervention) [3]. However, the quality of the evidence was ranked as low and very low, respectively.

The evidence supporting the success of dry or wet needling has low to moderate quality for the upper quarter and lower back, shoulders, or neck MPS [11, 12]. Methodological shortcomings and heterogeneity in the design, population, targeted muscles, and intervention prevent to draw strong conclusions. The small number of pooled studies in systematic reviews shows that the subject still requires further research [4, 6]. Particularly, follow-up beyond post-intervention is demanding to ascertain if improvements are maintained [4]. To the best of our knowledge, there is no randomized trial of local 5-HT_3-antagonists for the treatment of neck MPS. Also, a recent systematic review showed that there is no trial comparing the injection of local anesthetics in the head, neck, and shoulder regions with other interventions [6].

We conducted this double-blind trial to compare the clinical effects of lidocaine and granisetron injections into the trigger points of the upper trapezius muscle in patients with neck MPS. We hypothesized that lidocaine and granisetron would differ in their effects on neck pain and disability.

Methods

Design and setting

The study was registered at the Iranian Registry of Clinical Trials (IRCT) website http://www.irct.ir/, a WHO Primary Register setup, with the registration number of IRCT20200114046128N1. From October 2018 for 8 months we performed a double-blind randomized clinical trial with two parallel arms. The study was conducted in the Department of Physical Medicine and Rehabilitation at the Imam Reza Hospital; a teaching hospital affiliated with Aja University of Medical Sciences, Tehran, Iran. The department is a well-equipped setting with a high patient turnover, and the hospital is a large referral and subspecialty center.

Ethical considerations

The trial was carried out following the Declaration of Helsinki. Ethics approval was obtained from the Institutional Review Board of Aja University of Medical Sciences with the reference number of IR.AJAUMS.REC.1398.202. All participants gave signed written consent. They received verbal and written explanations of nature, possible side effects, and the purpose of the study. Patients were informed that they were free to withdraw from the study at any time.

Eligibility

We included men or women with MPS if their age was more than or equal to 18 years. The diagnosis of MPS was based on clinical findings. Participants were included, if they had neck or upper shoulder pain for at least one month with the self-assessed intensity of at least 3 cm on a 10 cm visual analog scale (VAS), at the time of presentation. They entered the study if we were able to find at least one trigger point in their upper trapezius muscle. Exclusion criteria were a history of systemic muscular or joint disease such as rheumatoid arthritis, fibromyalgia, ankylosing spondylitis, and stenosis of the spinal canal; any current medication use affecting the results of the study such as corticosteroids and muscle relaxant. We excluded women if they were pregnant or breastfeeding. None of our included patients had a known history of allergy to granisetron and lidocaine. People unwilling to participate were excluded from the study.

Recruitment

We recruited patients from the waiting list of the hospital. Consecutive patients with neck or shoulder pain were recruited. At first, patients were invited to attend a screening visit. The study phases and rationale were explained to all potential participants during the interview on the first visit. If a patient declined to participate, another was selected and invited in the same way until the needed sample was completed. At the screening visit, all patients filled two questionnaires about neck pain and disability. We reviewed documents from previous clinical diagnoses and carried out physical examinations, including detailed musculoskeletal evaluations with special attention to MPS and

exclusion of the differential diagnoses [1, 13]. Then, at a second visit, potential participants were presented to a consensus committee of the authors and underwent detailed assessments for eligibility as well as compliance. Next, eligible patients consented, were randomly allocated to one of the study groups, and immediately received their assigned intervention. The recruitment process lasted about 2 h for each individual. Figure 1 shows the flow of patients.

Protocols and interventions

Each trigger point received a single dose of 1 mL lidocaine 2% (Caspian Pharmaceutical Co, Tehran, Iran) or a single dose of 1 mg (in 1 mL) granisetron (Caspian Pharmaceutical Co, Tehran, Iran). The procedure was explained to the patient before the injection. The patient was positioned sitting upright, tender points identified, and the injection carried out. The upper trapezius area was palpated carefully for recognizing the location of trigger points [14]. We identify a trigger point within a taut band if a spot tenderness was present, if a mechanical stimulation of the spot caused referred pain or if snapping palpation of the taut reproduced local twitch response [15, 16]. The area was clean with alcohol, and then a 22-gauge needle was inserted into the trigger points at a 30-degree angle off the skin and aspirated. Next, the solution was injected into the sites using the Travell and Simsons' technique [17]. One milliliter solution was injected into each trigger point. For patients with multiple trigger points, two more tender ones were selected given that they were at least 3 cm apart. Therefore, none of the participants received more than 3 mL of the solutions.

At the end of the procedure, we applied a bag of ice covered with a towel for the patients to ease the pain for a short time. We instructed the patients to remain active while avoiding strenuous activity for three or four days, and to perform stretch exercise and massage of their upper trapezius muscles. One expert physiotherapist instructed all patients and showed them how to carry out the exercise. The patients were informed regarding pain or temporary numbness or discoloration around the injection sites, lightheadedness, and bleeding. Also, they were instructed not to use analgesic medications except for acetaminophen, if needed for 48 h. A study nurse phoned the patients within 24 h of the injections asking about the side-effects.

Outcome measures

We performed the measurements before the interventions; and one month and three months after the injections. The primary outcome

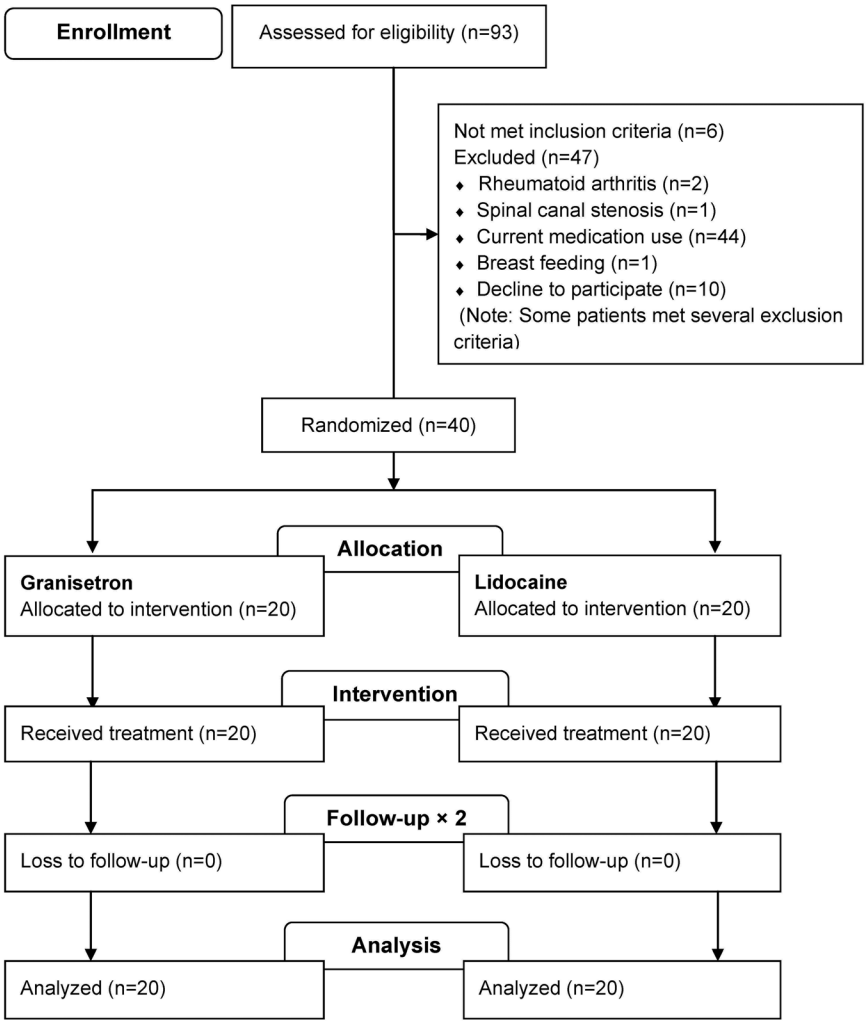

Figure 1: Participants' flow diagram.

was the Neck Disability Index (NDI) [18] and the secondary outcome measure was Neck Pain and Disability Scale (NPDS). We also measured the intensity of the neck pain within the last week of the baseline. A 10 cm visual analog scale was used to measure subjective pain rated from 0 (no pain) to 10 (most severe pain).

The NDI is a 10-item measurement tool asking about pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation. Each item has a six-point response scale ranging from 0 (no pain or limitation) to 5 (as much pain as possible or maximal limitation) in the activities. The NDI total score ranges from 0 to 50, as a higher score indicates greater disability. The score is calculated as total scored/total possible score (=50) × 100. Minimum detectable change (90% CI) is 5 points or 10 % points [19]. Researchers performed a secondary analysis on the data from a randomized clinical trial with 110 participants having a cervicogenic headache [20]. They reported that NDI exhibited excellent reliability with an intraclass correlation coefficient of 0.92 [0.46, 0.97]. In addition, they suggested that a 5.5-point reduction on the neck disability index after 4 weeks of intervention can be considered as clinically significant. The reliability and responsiveness of NDI have been confirmed in other studies including patients with neck pain of various etiologies [21–23].

The NPDS is a 20-item instrument to measure neck pain and related disability. Patients respond to each item using a 10 cm VAS. The subscales of the NPDS measures problems with neck movements, neck pain intensity, the effect of neck pain on emotion and cognition, and the level of interference with daily life activities. The questionnaire is easy to complete and simple to score and provides a validated tool to evaluate outcomes of treatments in patients with neck pain. The scores range from 0 to 5 for each item, and the total score ranges from 0 to 100 as higher scores indicate worse outcomes. It takes the patient about 5 min to mark all the items. The NPDS is widely used in the evaluation of neck pain [23–25]. A methodological systematic review was conducted to evaluate the translation procedures and measurement properties of cross-cultural adaptations of the NPDS [26]. Overall, 19 studies were included and 15 adaptations in 11 different languages studied. The study indicated that internal consistency, reliability, and construct validity had been evaluated in most eligible articles. It was concluded that Persian-Iranian, simplified-Chinese-2011, and Thai adaptations of NPDS had better quality than others concerning cross-cultural adaptation and measurement properties.

A good deal of research has been conducted to assess the validity, reliability, and responsiveness of the Persian-Iranian versions of NDI and NPDS in patients with neck pain [27, 24, 28, 29]. The estimated Cronbach's α coefficient for the NDI was 0.88 and the four subscales of the NPDS ranged from 0.74 to 0.94. The intraclass correlation coefficients of the NDI and NPDS subscales were excellent and ranged from 0.90 to 0.97 ($p<0.01$). Also, the two questionnaires were well correlated (Pearson correlation coefficients ranged from −0.31 to −0.70), and they were highly correlated with VAS (0.71 with NDI and 0.63 to 0.79 with NPDS subscales). It was concluded that the Iranian versions of NDI and NPDS are reliable and valid measurement tools for functional status in Persian-speaking patients with neck pain in Iran.

Sample size

There is one study in 2015 carried out by Christidis et al. focusing on the effect of granisetron on myofascial temporomandibular pain. However, they had not calculated a priori sample size or post-test effect size. Twenty participants in each group had been recruited to compare granisetron with saline [7]. They reported that at two-months follow-up the granisetron (n=16) and saline (n=8) groups were different for the outcome of a 30% reduction in weekly pain intensity (χ^2-test p=0.027). Our research team decided to base the sample size calculations on F-test for a longitudinal study. We calculated the sample size of our study for repeated measures ANOVA of pain data including within-between interactions with four times of measurements. Based on a medium effect size of 20% [30] for the F-test, a two-tailed p-value of less than 0.05 as statistically significant, a proposed power of 80%, and an actual power of 80.7%, a total of 36 participants were needed. We added four more people to ensure the study would be sufficiently powered for a 10% loss to follow-up. Therefore, a total of 40 participants were randomized into two groups (20 in each group). The calculations of sample size were carried out using R version 3.5.0 for windows (https://www.r-project.org/).

Randomization and blinding

For the random allocation of the two groups with the same size of 20 participants (40 patients in total), we used block randomization with different block sizes. The sizes of blocks were multiples of two and a divisor of 40 (2, 4, and 8). At first, the block sizes were selected randomly. Then, for each block, different permutations for equal group size were determined. Finally, one of the permutations was selected randomly. Random numbers were generated in an independent statistical room and with the help of a computer.

Our study was a double-blind randomized trial. The participants, investigators, and clinicians were unaware of the treatment assignments. The sequence of allocation was concealed from all investigators and participants with sequentially numbered sealed envelopes prepared at the statistical room. The envelopes contained cards with the group assignments type. A nurse who was neither involved in the intervention nor the assessments opened the envelope and prepared the solutions for injection based on the treatment assignments. The solution was then injected by a physician blinded to its content. Granisetron and lidocaine solutions were similar in their appearance. All follow-up evaluations were done by investigators blinded to the group assignment.

Statistical analyses

Results are presented as mean (SD) for continuous variables, and as absolute numbers (%) for categorical data. The means of the continuous variables were compared using paired and independent t-tests. The normality of the outcome variables was examined with the Shapiro–Wilk test and the homogeneity of variances was investigated with Levene's test. For mixed analysis of variance (ANOVA), the sphericity of the NDI and NPDS data were assessed with Mauchly's test, and if the assumption of sphericity was violated, the Greenhouse–Geisser correction was used for correcting the degrees of freedom. We used analysis of covariance (ANCOVA) test to control for the effects of age for comparing the two groups in neck pain and disability. The level of significance was set at two-tailed α=0.05. All data analyses were performed with R version 3.5.0 for windows. R is a well-known open-source environment for computing and graphics (https://www.r-project.org/).

Results

In total, we included 40 patients in our study. Figure 1 illustrates the numbers of participants for each group who were recruited, excluded, randomly assigned, received the treatments, and followed. All participants were compliant and there was no loss to follow-up in our study. Table 1 shows the baseline characteristics of each group and the total sample, as well. The distribution of the pain duration data was skewed to the right. Most of the participants (n=32) had pain within the last 24 months, and 12 had pain within the last 12 months. They were newly diagnosed as having MPS, often within the last several months. In addition, they commonly felt severe pain in their neck as was suggested by the reported intensity of neck pain in VAS. Examinations indicated that an upper trigger point was recognized in all the patients. The independent t-test showed that the two groups did not significantly differ with respect to the primary outcome, NDI [t(37.6)=−0.920, p=0.363, r=0.148]. The Levene's test showed that the variances of age were similar for the two groups, F(1, 38) $=3 \times 10^{-4}$, p=0.986. ANCOVA revealed that age was not a significant covariate for the NDI, F(1,37)=0.614, p=0.438.

There was a large and significant linear relation between NDI and NPDS (Pearson correlation coefficient r=0.95, 95% CI: 0.92 to 0.98, p<0.001). Table 2 shows the changes of the NDI and NPDS measurements from the baseline to three months post-injections. Three months after the interventions, NDI and NPDS were significantly lower than the baseline and the effect sizes are all large, varying from 0.86 to 0.99. Therefore, within-group analyses clearly showed that both granisetron and lidocaine were successful in reducing neck pain and disability.

Table 1: Participants' baseline characteristics.

Feature	Group		Total sample (n=40)
	Granisetron (n=20)	Lidocaine (n=20)	
Sex (female/male)	7/13	9/11	16/24
Age, year	55.6 (14.9)	44.7 (14.0)	50.1 (15.3)
Pain duration, month	18.7 (20.0)	17.6 (10.2)	18.1 (15.7)
Duration since the diagnosis of MPS, month	4.4 (3.9)	2.4 (1.9)	3.4 (3.2)
Neck pain in VAS	6.2 (1.1)	6.9 (1.4)	6.6 (1.3)
NDI percentage	53.7 (11.1)	57.1 (12.2)	55.4 (11.7)
Total NPDS	91 (26.7)	103.7 (19.9)	
Number of the trigger points	36	29	65
Upper	20	20	40
Middle	13	7	20
Lower	3	2	5

However, between-group analyses indicated that the neck pain responded more favorably to lidocaine than granisetron with medium effect sizes in Cohen's scale [30]. The mean difference of the changes in the primary outcome, NDI, between the two groups (13.2) surpassed the minimum detectable change of 5 points. Consequently, the difference is both statistically and clinically significant in favor of lidocaine.

Factorial ANOVA also showed that there was a significant main effect of group assignment on the changes of the NDI from the baseline to the third month of follow-up, F(1,36)=13.092, p<0.001; however, the main effect of sex and the interaction effect of sex × group were not significant F(1,36)=0.130, p=0.720, and F(1,96)=1.284, p=0.265, respectively (adjusted R^2=0.228). Overall, the difference in the NDI changes from the baseline to the third month between the two groups is related to the types of intervention rather than the sex composition of the groups.

Figures 2 and 3 illustrate the NDI percentage and NPDS values, respectively, before the interventions and at 1 and 3 months after the treatments. The figures show almost the same pattern. In one month post-intervention, the two groups are comparable. Thereafter, lidocaine lines continue to decline while granisetron lines remain steady.

We carried out a mixed ANOVA to compare the two groups in the NDI percentage throughout the study. The main effects of group was not significant F(1, 38)=1.151, p=0.270, η^2=0.02. The Mauchly's test showed that the assumption of sphericity was violated for time and group × time, W=0.411, p<0.001. Therefore, the degrees of freedom were corrected using Greenhouse–Geisser estimates of sphericity, ε=0.62. Time and the interaction effect of group × time were significant; F(1.2, 47.1)=204.068, p<0.001, η^2=0.52 and F(1.2, 47.1) =10.482, p<0.001, η^2=0.05, respectively. Similarly, mixed ANOVA of the NPDS data showed that group was not significant F(1,38)=0.021, p=0.885, η^2<0.001. However, time and group × time were significant predictors of the NPDS, F(1.1, 41.8)=286.416, p<0.001, η^2=0.66 and F(1.1, 41.8)=6.928, p=0.002, η^2=0.05, respectively. According to the mixed ANOVAs, lidocaine and granisetron were different in the pattern of their effects. Considering the three steps of measurements, the effects of group allocation on NDI and NPDS were significant in favor of lidocaine. In summary, the two interventions were similar within one month of therapy. But, afterward, they differ significantly in reducing pain and disability.

We did not find any instant adverse reactions after the interventions such as intolerable pain, numbness, bleeding, or dizziness. Commonly, the patients felt a transient pain at the sites of injections. All the participants were carefully examined at one month for any sign of the long-term side-

Table 2: Between- and within-group analyses for change in NDI and NPDS (DoF=degrees of freedom).

Feature	Group		t-Statistic (DoF)	p-Value	Effect size
	Granisetron (n=20)	Lidocaine (n=20)			
NDI percentage					
Baseline – 3 months, mean (SD) [95% CI]	20 (11.9) [14.4, 25.6]	33.2 (10.9) [28.1, 38.3]	−3.647 (37.7)	0.001	0.51
t-Statistic (DoF)	7.497 (19)	13.568 (19)			
p-Value	<0.001	<0.001			
Effect size	0.86	0.95			
Total NPDS					
Baseline – 3 months, mean (SD) [95% CI]	63.9 (26.7) [46.8, 81.1]	90.55 (19.9) [84.0, 97.1]	−3.36 (24.4)	0.006	0.52
t-Statistic (DoF)	7.808 (19)	29.118 (19)			
p-Value	<0.001	<0.001			
Effect size	0.87	0.99			

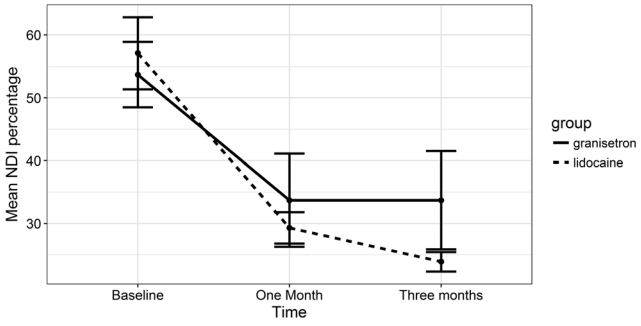

Figure 2: Changes of the NDI percentage throughout the study for granisetron (n=20) and lidocaine (n=20) groups.

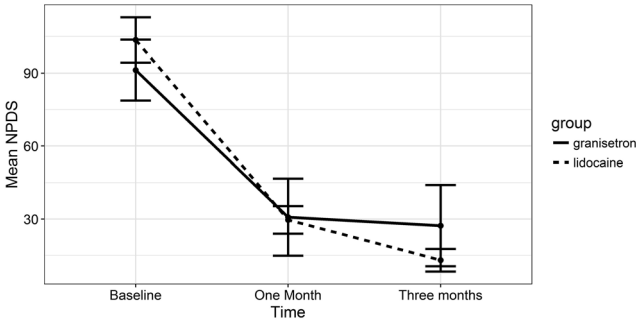

Figure 3: Changes of the NPDS throughout the study for granisetron (n=20) and lidocaine (n=20) groups.

effects such as infection. Overall, no significant side-effect was recognized for both granisetron and lidocaine groups.

Discussion

We conducted this study to compare the effects of granisetron with lidocaine on neck pain and disability in two groups of people with neck MPS. We found that both interventions significantly affect the symptoms comparably in one month. Participants in the two groups experienced a steep decrease in pain and disability at that period. However, a three-month follow-up of patients revealed that the favorable effects of granisetron became steady, while for lidocaine, the pain and disability continued to decrease. It should be noticed that participants carried out stretch exercise and this might cause the benefits to last for three months. Meanwhile, both groups performed the exercise and therefore, it could hardly be a source of the discrepancy between the two groups.

Our experience showed that both interventions were well-tolerated by the patients, although a transient pain at the site of injections was a common complaint. The results are consistent with the findings reported in the literature regarding the effects of lidocaine or the effects of granisetron injections to trigger points of MPS. Though, to our knowledge and based on systematic reviews [6], this trial is unique in comparing the efficacy of the two injective medications for MPS.

The underlying mechanism of MPS is still poorly understood [1]. It has been suggested that muscular tension decreases blood flow and oxygen level and subsequently stimulates the release of pain mediators. The increase in pain mediators is associated with the activation of nociceptive receptors and eventually with the emergence of the symptoms and signs [3]. In addition, slow and repetitive muscle contractions cause the formation of taut bands and trigger points [1]. Trigger points send nociceptive sub-threshold signals to the dorsal horn of the spinal cord to sensitize the central nervous system. Lidocaine modifies the nociceptive pain threshold by acting on sodium channels. The goal of the treatment is to release trigger points. Our lidocaine group showed more favorable outcomes over three months. This is not

achieved by the short-lasting anesthetic effect of lidocaine. The more stable effects of lidocaine could be attributed to a greater release of trigger points compared with granisetron in patients with MPS. However, the histochemical mechanism of the long-lasting effects of lidocaine demands another research. Meanwhile, the C-fiber release of neuropeptides such as serotonin activates a neurogenic inflammatory mechanism in trigger points [1]. Serotonin is released peripherally from platelets and mast cells because of tissue damage or ischemia, as well. So, an antagonist of serotonin receptors like granisetron has the potential to increase the pain threshold [7].

Trials have been conducted to compare lidocaine injection to trigger points with other injectable medications or with dry needling. However, they failed to reproduce the same results. In a previous single-blind trial on 23 patients with MPS, trigger point injection of botulinum toxin type A (n=9) and lidocaine (n=10) were compared with dry needling (n=10) [31]. The patients were assessed before, and 48 weeks after the interventions. For the lidocaine group, 1 mL of 0.5% lidocaine was administered to each trigger point. The patients were asked to carry out a home exercise program. At the end of the study, the pain score was the lowest in the lidocaine group. Besides, both lidocaine and botulinum groups showed an increase in their quality of life scores.

In another study, Ay et al. compared the efficacy of trigger point injection of 2 mL of 1% lidocaine (n=40) and dry needling (n=40) [32]. Both groups showed a significant reduction in pain scores, and significant improvement in the cervical range of motion 4 and 12 weeks post-intervention. However, there was no significant between-group difference in pain intensity throughout the study. It was concluded that exercise with local anesthetic injection and dry needling is effective for neck MPS.

More recently, a trial was carried out by Choi et al. for comparing lidocaine alone (n=31) with lidocaine and hyaluronidase co-injection (n=30) to trigger points of patients with MPS [33]. All the participants received 3.2 mL 0.5% lidocaine and were followed for 14 days with the NDI and several other outcome measures. The results showed that both groups experienced favorable outcomes without significant between-group differences. The only difference was that patients with co-injection of hyaluronidase showed better outcomes at day one. In a randomized controlled trial, researchers compared granisetron (n=20) with isotonic saline (n=20) injections to the trigger point of patients with myofascial temporomandibular disorders [7]. The participants in the intervention group received three doses of 3 mg granisetron one week apart and were followed for six months. The pain decreased significantly at all follow-up steps in the granisetron group compared with the control. They concluded that granisetron is beneficial for the patients in the short- and long-term post-injection.

Data for the administration of granisetron to trigger points are less than those of lidocaine. A recent systematic review with meta-analysis was carried out to assess the efficacy of local anesthetic trigger point injections in the head, neck, and shoulder compared to dry needling, placebo, and other interventions [6]. The primary outcome was the intensity of pain in VAS. Fifteen randomized controlled trials were included with 884 patients with MPS. The study suggested that while local anesthetics significantly reduce the pain intensity in the short-term, evidence was of low quality. Additional studies were warranted to strengthen the existed evidence.

Our results are in accordance with those of other studies where both lidocaine and granisetron were beneficial for injection to muscle trigger points of patients with MPS. One meta-analysis of randomized trials ranked treatments of MPS according to their efficacy in reducing pain intensity [3]. Lidocaine was more effective than granisetron within 20 days post-injection. For long term follow-ups, lidocaine was reported as the best needling therapy. However, in that study, the data were collected through different and independent trials. In addition, the evidence was assessed as low quality. Our trial was the first to directly compare the efficacy of granisetron with lidocaine in the treatment of MPS.

We used two standard and valid questionnaires to assess the outcomes of the interventions. Also, we enjoyed high patients' compliance. Our analyses were straightforward, the sample size was large enough to maintain the power of the statistical tests, and the effect sizes were remarkable. Meanwhile, we did not investigate the optimum dose, combination therapy, and the effects of the interventions in the long-term. We did not have a placebo control group and were not able to recognize any placebo effect for the injections. However, favorable results could hardly be attributed to the placebo effect. Because the benefits continued for at least three months, and they were observed in two outcomes. Though, any possible placebo effect could be evaluated in a further controlled trial with particular attention given to the ethical considerations. It should be noticed that in our study, both lidocaine and granisetron groups carried out stretching and exercise programs. Further research is needed to compare each pure intervention with exercise programs and to recognize if there is any Hawthorne effect biasing within-group analyses toward better results.

Conclusion

In conclusion, our study showed that both lidocaine and granisetron injections are effective and safe for the treatment of neck MPS. Lidocaine is more effective than granisetron for injecting to the trigger points in patients with MPS of the upper trapezius muscle. A single dose of 1 mL lidocaine 2% injected to the trigger points reduces the neck pain and disability quickly. The injection plus performing stretch exercise and massage of upper trapezius muscles caused the benefits remain at least for three months. The injections, if properly done are well-tolerated by patients, although a transient pain at the site of injections is a common complaint.

Research funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions: ZR contributed to the design and development of the study protocols, supervised physical examinations, and contributed to the decision on eligibility. HE helped with the literature review and performed statistical analyses. RKM contributed to the literature review and design and helped with statistical analyses. FV and RM participated in the design of the study, guided the recruitment process, interviewed patients, and performed physical examinations. SN conceptualized and designed the study, guided the development of the protocols and performed the injections, helped with the decision on patients' eligibility, and the interpretation of the results. All the authors participated in drafting and its final approval.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethics approval: Obtained from the Institutional Review Board of Aja University of Medical Sciences with the Ethics Committee reference number of IR.AJAUMS.REC.1398.202.

Registration: Iranian Registry of Clinical Trials (IRCT) website http://www.irct.ir/, a WHO Primary Register setup, with registration code: IRCTID: **IRCT20200114046128N1**.

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